

Concurrent Cerebral Toxoplasmosis and CMV Retinitis in an HIV-positive Patient

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### Case Report:

A 35-year-old previously healthy female recently emigrated from Honduras and presented with a five-day history of sudden onset decreased vision in her right eye, pain with extraocular movements, fevers, and a three-day history of right upper and lower extremity weakness and numbness. On exam, she was afebrile and mental status was normal. She had no light perception in the right eye, a right relative afferent pupillary defect, right lower facial weakness, 4/5 strength of proximal and distal right upper and lower extremities, and decreased sensation in the right face, arm, and leg.

Her fundoscopic exam revealed severe optic disc edema, cotton wool spots, extensive flame-shaped peripapillary and intraretinal hemorrhages, and superior retinal pallor secondary to a branch retinal artery occlusion in the right eye (Figure 1). The nasal periphery of the left eye retina demonstrated patchy, white lesions.

MRI of the brain with and without contrast showed scattered ring-enhancing lesions throughout the superficial and deep gray matter including the bilateral thalami and right globus pallidus with slight mass effect (Figure 2), right optic nerve enhancement, and neck/parotid lymphadenopathy.

Routine admission laboratory testing was remarkable for serum leukopenia ( $WBC\ 2.8 \times 10^9/L$ ) and neutropenia ( $ANC\ 1.1 \times 10^9/L$ ). Cerebrospinal fluid (CSF) studies revealed no pleocytosis, normal protein (320 mg/L), low glucose (1.6 mmol/L), negative VDRL, negative cytomegalovirus (CMV) PCR, negative gram stain and culture, normal ACE (0.0119 mcKat/L), and an elevated IgG index (0.99). Blood cultures, Mantoux tuberculin skin test, sputum AFB culture, fungal culture, Cryptococcal antigen, and treponemal antibody testing were negative. Chest CT showed no abnormalities. Western blot analysis was positive for HIV-1 with a CD4 count of 3 cells/mm<sup>3</sup> and a viral load of 470,000 copies/mL.

Serum CMV PCR and toxoplasmosis PCR and IgG were positive. She underwent diagnostic anterior chamber paracentesis and was treated with bilateral intravitreal ganciclovir injections, although anterior chamber CMV PCR and varicella zoster virus PCR later returned negative. She was treated with intravenous ganciclovir and oral sulfamethoxazole/trimethoprim for CMV and toxoplasmosis, respectively, as well as azithromycin for MAC prophylaxis. She was started on antiretroviral therapy with elvitegravir-cobicistat-emtricitabine-tenofovir (Genvoya). One month after presentation, her HIV viral load was 110 copies/mL, her right sided motor/sensory deficits and retinitis and optic disc edema were improving, but her right eye visual acuity remained at no light perception. The patient was subsequently lost to follow-up.

### Discussion:

The patient's presentation with right eye vision loss, pain with eye movement, and right-sided weakness/numbness were initially concerning for demyelinating disease. However, her brain lesions in the gray matter were not characteristic of demyelination, and her fundus findings suggested an alternative etiology. Her subjective fevers, leukopenia, neutropenia, and recent immigration heightened awareness of infectious causes, such as dengue fever, chikungunya, Zika virus, Chagas disease, toxoplasmosis, cytomegalovirus, neurocysticercosis, neurosyphilis, tuberculosis, and human immunodeficiency virus (HIV) with associated opportunistic infection.<sup>1</sup> Inflammatory, infectious, and neoplastic conditions, such as neurosarcoidosis, neurosyphilis,

atypical bacterial or fungal meningitis, granulomatosis with polyangiitis, lymphoma, and opportunistic infections were also considered.

A CD4 cell count of  $<200/\text{mm}^3$  with HIV positive status confirmed acquired immunodeficiency syndrome (AIDS), and conferred an increased risk for central nervous system (CNS) opportunistic infection, demyelination, and malignancy, with the most common being toxoplasmosis, CNS lymphoma, progressive multifocal leukoencephalopathy (PML), HIV encephalitis, and CMV infection. These can be partially differentiated on the basis of MRI features (Table 1).<sup>2</sup> Opportunistic infections that commonly affect the eye are summarized in Table 2.<sup>3</sup> The presence of multiple ring-enhancing lesions in the bilateral thalami and right globus pallidus on brain MRI is characteristic of toxoplasmosis (Figure 2). The patient's optic disc edema, optic nerve enhancement on MRI, retinal vasculitis, and retinal ischemia are characteristic of CMV retinitis with optic neuritis (Figure 1).

CMV retinitis is the most common ocular opportunistic infection in AIDS patients with a CD4 cell count of  $<50/\text{mm}^3$ , although its incidence has decreased with the use of antiretroviral therapy (ART).<sup>4</sup> CMV retinitis results from hematogenous spread of CMV and low CD4 counts, which permit CMV replication.<sup>4</sup> CMV retinitis can cause decreased vision, floaters, photopsias, retinal detachment, or even complete vision loss.<sup>5</sup> CMV PCR, blood antigen, and blood culture testing have poor sensitivity and specificity in determining end-organ disease.<sup>4</sup> A false negative anterior chamber paracentesis CMV PCR is likely in this case because of classic CMV fundus findings, positive serum CMV PCR, and her rapid response to intravitreal and intravenous ganciclovir. The patient's ocular findings were inconsistent with toxoplasmosis, which presents with retinochoroiditis and vitreous reaction, none of which were seen in this patient.<sup>6</sup> Treatment involves ganciclovir and ART in cases associated with HIV.<sup>7</sup> For patients with lesions near the fovea or optic nerve head, intravitreal ganciclovir or foscarnet in addition to systemic CMV therapy is recommended. Frequent funduscopy examinations by an ophthalmologist are needed to monitor for adequacy of response to treatment.<sup>7</sup> Portions of the retina damaged by CMV do not regenerate, therefore, the goal of treatment is to prevent progression.<sup>5</sup>

Toxoplasmosis is the most common CNS opportunistic infection in AIDS patients with a CD4 cell count  $<100/\text{mm}^3$  who are not on prophylaxis.<sup>8</sup> Like CMV, the incidence of toxoplasmosis has decreased with ART. Symptoms include fever, headache, confusion, focal neurologic deficits, as well as extracerebral manifestations such as pneumonitis and retinochoroiditis.<sup>8</sup> The diagnosis is clinical, and may be aided by the presence of toxoplasma serum IgG antibodies and multiple ring-enhancing lesions on brain MRI.<sup>9</sup> Stereotactic brain biopsy is the gold standard for diagnosis of brain lesions, but may cause significant morbidity. Treatment includes sulfadiazine/pyrimethamine induction therapy for six weeks followed by maintenance therapy.<sup>7</sup> Clinical improvement and a reduction in lesion size are expected within two weeks of treatment commencement.<sup>8</sup>

The presence of active CMV retinitis and cerebral toxoplasmosis in the same patient at the same time emphasizes the importance of a thorough evaluation in patients with opportunistic infection and that a single disease entity may not sufficiently explain a patient's clinical presentation. Being familiar with the typical clinical presentation of each entity has the potential to decrease morbidity associated with delayed diagnosis and treatment.

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Table 1. Differentiation of common CNS opportunistic infections based on brain MRI findings<sup>2</sup>

<b>Infection</b>	<b>Focal</b>	<b>Enhancement</b>	<b>Location of lesion</b>	<b>Other tests</b>
Toxoplasmosis	Multifocal	Ring-enhancing	Frontal and parietal lobes, thalamus, basal ganglia, gray/white matter interface	Serum PCR
CNS lymphoma	Solitary or multifocal, >4cm	Ring-enhancing	Corpus callosum, periventricular, periependymal areas	CSF cytology
Progressive multifocal leukoencephalopathy (PML)	Multifocal, bilateral, asymmetric	No enhancement	Periventricular and subcortical white matter	Serum PCR JC virus
HIV encephalitis	Multifocal, bilateral, symmetric	No enhancement	Subcortical white matter	N/A
Cytomegalovirus	Multifocal	Rare enhancement	Cortex, basal ganglia, brainstem, cerebellum, ventricular enlargement	Serum PCR

Table 2. Differentiation of ocular opportunistic infections based on funduscopy findings<sup>3</sup>

<b>Infection</b>	<b>Ophthalmologic exam findings</b>
Cytomegalovirus	Severe optic disc edema, cotton wool spots, widespread retinal hemorrhage and necrosis
Toxoplasma	Fluffy areas of retinal whitening, vitritis, less retinal hemorrhage than CMV
Candida	Fluffy, white, superficial mounds that extend into the vitreous
Bacterial retinitis	Multifocal, yellow-white retinal lesions, subretinal fluid, exudate
Cryptococcus	Multiple, discrete yellow spots in the choroid and retina, papilledema
Pneumocystis	Multiple, yellow-white, round or ovoid choroid lesions, choroidal necrosis
Varicella	Peripheral retinal whitening that leads to necrosis, retinal detachment